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Psychiatric Stability of INGREZZA in Adults with Tardive Dyskinesia

Thank you for contacting Neurocrine Biosciences with your unsolicited Medical Information request regarding the impact of INGREZZA® (valbenazine) capsules on psychiatric stability.

INGREZZA is a vesicular monoamine transporter 2 (VMAT2) inhibitor indicated for the treatment of adults with tardive dyskinesia.[1]

KINECT 3: Double Blind Placebo Controlled (DBPC) Study

KINECT 3 was a randomized DBPC Phase 3 study that assessed the efficacy, safety, and tolerability of valbenazine (VBZ) for the treatment of adults with tardive dyskinesia (TD). The primary efficacy endpoint was the mean change from baseline (CFB) at end of Week 6 in the AIMS dyskinesia total score (sum of Items 1-7) for VBZ 80 mg vs. placebo. Participants were required to be medically and psychiatrically stable. Participants were excluded from the study if they had a comorbid movement disorder more prominent than TD, known history of substance abuse, violent or suicidal behavior, neuroleptic malignant syndrome, or prolonged QT syndrome. There were 234 male and female participants randomized 1:1:1 to receive placebo, VBZ 40 mg, or VBZ 80 mg once daily for a 6 week period.[2]

Participants were assessed for psychiatric stability throughout the study using the following scales: Positive and Negative Syndrome Scale (PANSS), Calgary Depression Scale for Schizophrenia (CDSS), Young Mania Rating Scale (YMRS), Montgomery-Åsberg Depression Rating Scale (MADRS), and the Columbia-Suicide Severity Rating Scale (C-SSRS). Demographics were similar across treatment groups. Mean psychiatric scale scores generally remained stable during the study (see **Table 1**). No safety signal was detected for suicidality based on treatment-emergent adverse events (TEAEs) and C-SSRS responses.[2]

Table 1. Psychiatric Scale Scores Change from Baseline to Week 6 (Safety Population[†])

Psychiatric Scale Scores, LS mean (SEM)	Placebo	VBZ 40 mg	VBZ 80 mg
PANSS Positive Symptoms score[a]	-0.0 (0.5)	-0.5 (0.3)	-0.3 (0.3)
PANSS Negative Symptoms score[a]	-0.0 (0.5)	-0.0 (0.4)	0.5 (0.4)
PANSS General Psychopathology score[a]	-0.2 (0.8)	-1.3 (0.8)	-0.8 (0.5)
CDSS score[a]	-0.1 (0.3)	-0.5 (0.3)	-0.4 (0.3)
YMRS score[b]	0.1 (0.5)	-0.3 (0.5)	-1.1 (0.5)
MADRS score[b]	1.0 (0.9)	0.5 (1.1)	-1.7 (0.9)

[†]The safety population included all participants who underwent randomized assignment to treatment, received at least one dose of study drug, and had at least one postbaseline safety assessment; [a]placebo n=50, VBZ 40 mg=48, VBZ 80 mg=52; [b] placebo n=26, VBZ 40 mg=24, VBZ 80 mg=27. CDSS, Calgary Depression Scale for Schizophrenia; LS, least squares; MADRS, Montgomery-Asberg Depression Rating Scale; PANSS, Positive and Negative Syndrome Scale; SEM, standard error of the mean; VBZ, valbenazine; YMRS, Young Mania Rating Scale.

The most common treatment-emergent adverse events for valbenazine (both dosage groups combined) and placebo in the KINECT 3 study were somnolence (5.3% and 3.9%, respectively), akathisia (3.3% and 1.3%, respectively), and dry mouth (3.3% and 1.3% respectively), while suicidal ideation was the most common in the placebo group (5.3% compared with 2.6% in the valbenazine groups combined).[3]

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Pooled Long-term Data

To examine the safety profile of long-term exposure to VBZ in adults with TD, a pooled analysis of participants in two Phase 3 studies: KINECT 3 (NCT02274558) and KINECT 4 (NCT02405091) was performed (pooled long-term population).[4]

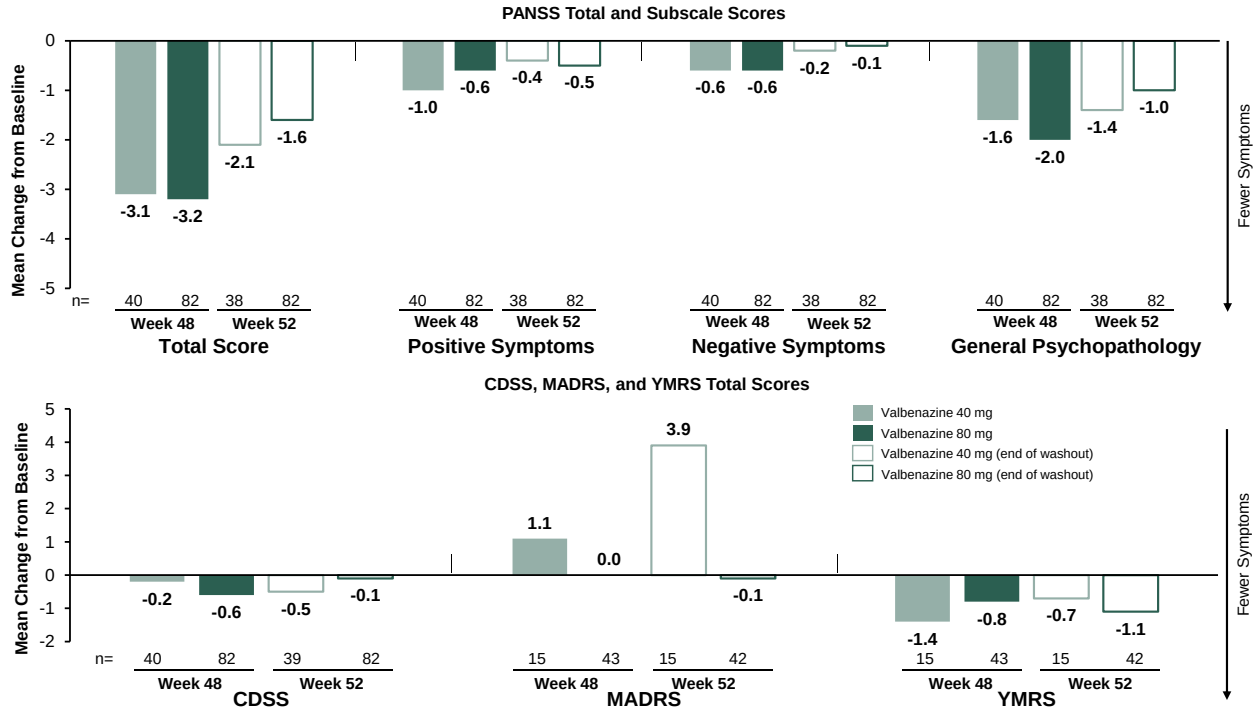
Participants who completed the KINECT 3 DBPC period continued with a 42-week double-blind VBZ extension (VE) period (Week 48) and a 4-week drug-free follow-up period (Week 52). KINECT 4 (NCT02405091) was an open-label, long-term (48-week open-label treatment period and a 4-week drug-free follow-up period) Phase 3 study to evaluate the safety and tolerability of VBZ 40 mg and 80 mg in adults with TD. Pooled data from KINECT 3 and KINECT 4 included a 40 mg dose group (included the 40 mg group from KINECT 3 and participants from KINECT 4 who did not have a dose escalation to 80 mg) and an 80 mg dose group (included the 80 mg group from KINECT 3 and participants from KINECT 4 who were escalated to 80 mg at Week 4). Participants who initially received placebo in the KINECT 3 study were excluded from the analyses.[4]

Psychiatric stability was assessed in the pooled long-term population (KINECT 3 and KINECT 4) using the following scales: CDSS and PANSS in participants with schizophrenia/schizoaffective disorder; MADRS and YMRS in participants with a mood disorder. All data were analyzed descriptively, with no statistical testing between VBZ dose groups.[4]

Overall, 304 participants were included in the pooled long-term population. Baseline characteristics were generally similar between VBZ dose groups. In the pooled long-term population, mean changes from baseline to Week 48 (end of treatment) and Week 52 (end of 4-week drug-free period) in PANSS, CDSS, MADRS, and YMRS scores indicated that psychiatric status generally remained stable in both VBZ dose groups (Figure 1).[4]

In the pooled long-term population, 71.7% of participants had ≥1 TEAE at any time during the study, and 15.5% discontinued due to an adverse event. Headache and urinary tract infection (8.9% each) were the most commonly reported TEAEs in all participants. Additionally, there were no clinically important changes in laboratory parameters, vital signs, or ECG parameters.[4]

Figure 1: Mean Changes from Baseline in Psychiatric Scale Scores (Pooled Long-Term Population)



CDSS, Calgary Depression Scale for Schizophrenia; MADRS, Montgomery-Åsberg Depression Rating Scale; PANSS, Positive and Negative Syndrome Scale; YMRS, Young Mania Rating Scale

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This letter and the enclosed material are provided in response to your unsolicited medical information inquiry. Please feel free to contact Neurocrine Medical Information at (877) 641-3461 or medinfo@neurocrine.com if you would like to request additional information.

References

1. INGREZZA [package insert]. San Diego, CA: Neurocrine Biosciences, Inc.
2. Factor SA, et al. KINECT 3: A randomized, double-blind, placebo-controlled phase 3 trial of valbenazine (NBI-98854) for tardive dyskinesia. Poster presented at the International Congress of Parkinson's Disease and Movement Disorders Society; June 19-23, 2016; Berlin, Germany.
3. Hauser RA, et al. KINECT 3: A phase 3 randomized, double-blind, placebo-controlled trial of valbenazine for tardive dyskinesia. Am J Psychiatry. 2017;174(5):476-484.
4. Marder SR, et al. Long-term safety and tolerability of once-daily valbenazine in patients with tardive dyskinesia. Poster presented at the US Psychiatric and Mental Health Congress; October 25-28, 2018; Orlando, FL.

Enclosures

A. INGREZZA [package insert]. San Diego, CA: Neurocrine Biosciences, Inc.
B. Factor SA, et al. KINECT 3: A randomized, double-blind, placebo-controlled phase 3 trial of valbenazine (NBI-98854) for tardive dyskinesia. Poster presented at the International Congress of Parkinson's Disease and Movement Disorders Society; June 19-23, 2016; Berlin, Germany.
C. Marder SR, et al. Long-term safety and tolerability of once-daily valbenazine in patients with tardive dyskinesia. Poster presented at the US Psychiatric and Mental Health Congress; October 25-28, 2018; Orlando, FL.